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Use of Diphtheria Toxoid-Tetanus Toxoid-Acellular Per Five-Dose Series

Supplemental Recommendations of the Advisory Committee on Immuniza

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Use of Diphtheria Toxoid-Tetanus Toxoid-Acellular Pertussis Vaccine as a Five-Dose Series

Supplemental Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

Four vaccines containing diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) are currently licensed young children. As of October 2000, two products, ACEL-IMUNE® (a product of Lederle Laboratories) and Tripedia® dose DTaP vaccination series. Two other vaccines, Infanrix® (SmithKline Beecham Biologicals) and Certiva™ (North four doses of the vaccination series, beginning with the primary series at ages 2, 4, and 6 months, and for completing t series with diphtheria and tetanus toxoids and whole-cell pertussis vaccine. This report supplements the statement fro Practices regarding use of acellular pertussis vaccines and summarizes data regarding reactogenicity of acellular per and fifth consecutive doses. Increases in the frequency and magnitude of local reactions at the injection site with incre licensed DTaP vaccines. Extensive swelling of the injected limb, sometimes involving the entire thigh or upper arm, af vaccines has been demonstrated for multiple products from different manufacturers. Because data are insufficient reg

using DTaP vaccines from different manufacturers in a mixed sequence, ACIP continues to recommend that, whenever for all doses in the vaccination series. When the vaccine provider does not know or does not have available the type of licensed DTaP vaccines can be used to complete the vaccine series.

INTRODUCTION

Four vaccines containing diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) are licensed for use am ACEL-IMUNE® (a product of Lederle Laboratories) and Tripedia® (Aventis Pasteur, Inc.) are licensed for use as the f licensed vaccines are approved for use for the first four doses of the five-dose series, beginning at ages 2, 4, and 6 mon dose series is anticipated. This report supplements previous recommendations regarding use of DTaP (*1*) and summari Practices (ACIP) recommendations regarding DTaP vaccines as a five-consecutive--dose series.

REACTOGENICITY OF DTaP VACCINES WHEN ADMINISTERED AS FOURTH AND FIFTI

Data regarding use of a single DTaP vaccine for the complete five-dose series are limited, but available data demonstra magnitude of local reactions after the fourth and fifth doses. Increases in the frequency of fever after the fourth dose ha frequencies of other systemic reactions (e.g., fretfulness, drowsiness, or decreased appetite) have not been observed. D and fifth doses, acellular pertussis vaccines remain the preferred vaccines for preventing pertussis, diphtheria, and teta profile when compared with whole-cell pertussis vaccines (*2--5*).

Adverse Reactions After the Fourth Dose of DTaP When Administered as a Four-Dose Series

Increases in erythema, swelling, and pain at the injection site and increases in fever have been reported with the fourth the currently licensed DTaP vaccines. These reactions typically have onset within 2 days of vaccination and resolve co

During 1991--1994, reactogenicity of ACEL-IMUNE administered as a four-dose series was assessed in an efficacy st tetanus toxoids and whole-cell pertussis vaccine (DTP) components of the study were randomized and double-blinded standard diary cards for 72 hours after each dose. Of 3,991 children who received the fourth dose of ACEL-IMUNE, 1 9% experienced induration ≥0.9 in. (≥2.4 cm). After the first dose, only 2% of recipients were reported as experiencing ≥100.4 F (≥38 C) was reported for 7% of recipients of the first dose, but after the fourth dose, 26% of recipients experi

In an open-label trial (i.e., a study in which researchers and subjects know what vaccine and dose is being administered previously received Tripedia at ages 2, 4, and 6 months received a fourth dose at age 1520 months (*9*). Reactions were daily thereafter for 14 days, and parents were asked to record daily on a standardized diary the presence or absence of children receiving the fourth dose, 5.5% experienced fever >101 F (>38.3 C) within 72 hours of vaccination; 30.3%, in injection site swelling ≥1 in. (≥2.54 cm); and 19.3%, injection site pain (*9*). In contrast, during the primary series study F (>38.3 C) after the first dose; 2%, erythema >1 in. (>2.54 cm); 2%, swelling >1 in. (>2.54 cm); and 10%, tenderness

Of 22,505 children who had received three doses of Infanrix® (SmithKline Beecham Biologicals) at ages 3, 4, and 5 m during April 1993--November 1994, 5,361 received a fourth dose at age 10--36 months (*11*). Standardized diaries repo vaccination were available for 1,809 children who had received the fourth dose. Age range of this subset of children w and fever increased with successive doses. Redness >0.8 in. (>2 cm) increased from 0% after the first dose to 13.8% a 0% to 11.4%; pain, from 2.0% to 26.3%; and fever ≥100.4 F (≥38 C), from 6.3% to 26.4% (*1113*).

Increases in the reactogenicity of the fourth dose of Certiva™ (North American Vaccine, Inc.) also have been reported infants, a subset of >2,200 who received Certiva as a three-dose primary series during an open-label trial in the United standardized diary cards and telephone follow-up. Fever ≥100.4 F (≥38 C) within 72 hours of vaccination increased in with fever reported among 1.5% of first-dose recipients and 10.5% of fourth-dose recipients. Frequency of redness ≥1. dose to 5.7% after the fourth dose; swelling ≥1.2 in. (≥3 cm), from 0.6% to 4.5%; and tenderness or pain (any), from 5

Adverse Reactions After the Fifth Dose of DTaP When Administered as a Five-Dose Series

Data regarding the reactogenicity of a fifth dose of DTaP administered after four doses of the DTaP vaccine are limite licensed DTaP vaccines. These data demonstrate further increases in the local reactogenicity of the fifth dose compare regarding the frequency of adverse events after a fifth dose of Certiva.

Data have been summarized from four clinical trials in the United States and Germany, during which 357 infants recei received four previous doses of the same vaccine. Case definitions of substantial erythema and induration varied by pr (>2.4 cm). However, substantial erythema within 72 hours after the fifth dose was reported for 20% of recipients; subs (*8*).

In a study in Germany during March--September 1998, of 580 children who received a fifth dose of Tripedia after fou experienced redness >2 in. (>5 cm) within 3 days of receipt of vaccine; 25.0% experienced swelling >2 in. (>5 cm); ar the arm was moved) (*15*, Aventis Pasteur, Inc., unpublished data, January 2000). During a safety study in Germany, 41 four previous doses of the same vaccine. During the 3 days after vaccination, redness ≥2 in. (≥5 cm) was reported for 3 20.7%; and grade 3 pain (i.e., pain that prevented everyday activities and necessitated medical advice) for 1.6% of the completed (SmithKline Beecham Biologicals, unpublished data, February 2000).

Limb Swelling After Booster Doses of DTaP

Swelling involving the entire thigh or upper arm has been reported after booster doses of different acellular pertussis v among recipients of a booster dose of JNIH-6 (a two-component acellular pertussis vaccine produced by Biken [Japan component contained in Tripedia). During a study performed in Sweden during the 1980s, children who had previousl pertussis vaccine at age 6--8 months received a booster dose deep subcutaneously of the same vaccine at age 2 years. C reactions, including swelling of the entire thigh (*16*), although administration of vaccine subcutaneously could have in

Occurrence of extensive swelling involving the entire thigh of vaccinated children was reported among DTaP recipien April 1993--November 1994, in which children who had previously received Infanrix at ages 3, 4, and 5 months receiv Standardized diaries were available for 1,809 children, with data collected regarding the occurrence of specific solicite Parents of the remaining 3,498 children were asked to report any symptoms occurring during the 28 days after vaccina 5,361 vaccinees, an increase in thigh circumference was reported as an unsolicited reaction for 62 vaccinees (45 in the 1.2%). One of six centers participating in the study accounted for a majority of these reports; at that center, this reactio Among 17 children whose thighs were measured, the mean increase in circumference was 0.9 in. (2.2 cm) (range: 0.2- hours of booster dose administration for 51 of 62 children; the mean duration of swelling was 3.9 days (range: 1--7 da interfered with walking; but for the majority of children, no limitation of activity was experienced. None of the childre applied was reported for 51% of the children, and itching was observed among a limited number of children (*11*).

In an analysis of the fourth- and fifth-dose follow-up studies from the Multicenter Acellular Pertussis Trial (MAPT) th limb swelling was reported as an unsolicited reaction for 20 (2.0%) of 1,015 children who received four consecutive d was reported for 1 of 16 children receiving four consecutive doses of DTP and for 0 of 246 children receiving a booste children experiencing entire thigh swelling after the fourth dose, 70% were described as irritable, compared with 37% entire thigh swelling. Erythema was reported for 60% of the vaccinees and pain for 60%; the corresponding frequencie were 29% and 30%, respectively. Fever >100 F (>37.8 C) was reported for approximately 25% of both groups. Among was judged to be mild for 7, moderate for 2, and severe for 3; pain was not reported for 8 of these 20 children. Of eigh experienced moderate or severe pain. A total of 12 children experienced swelling that began on day 2 or 3, none of wh thigh swelling resolved completely and without sequelae among all 20 children (duration: 1--4 days among 11 childre dose recipients, 0 of 121 children who had received the same DTaP vaccine experienced swelling of the entire upper a children (2.7%) who had received different DTaP vaccines during the five-dose series. Although the numbers of childr follow-up studies were limited, extensive limb swelling occurred after receipt of a fourth dose of 9 of the 12 DTaP vac

Recent studies of the fifth dose of Tripedia and Infanrix have also identified cases of extensive limb swelling. During a March--September 1998, swelling of the entire upper arm was reported as an unsolicited reaction for 14 of 490 childre (Aventis Pasteur, Inc., unpublished data, January 2000). For 13 of the 14 children, swelling began within 3 days of vac for 10 of the 14 (71.4%) vaccinees, pain for 5 (35.7%), and fussiness for 2 (14.3%). Pain was graded as mild for all ch fever >100.4 F (>38 C), and only two children were evaluated during an office visit. Median duration of swelling was unpublished data, January 2000). During an open-label trial in Germany of Infanrix as a fifth dose after four doses of I possibility of limb swelling (SmithKline Beecham Biologicals, unpublished data, February and May 2000). Although diary cards, parents or caretakers were asked to contact the investigators if their children experienced such a reaction. contacted the investigators to report that their children had experienced swelling. A total of 3 of the 26 children (11%) axillarily or orally or ≥100.4 F (≥38 C) when measured rectally. Other associated symptoms included pain for 23 (88.5 occurred for 26 (100%) vaccinees and was diffuse for 17. Warmth was experienced by 21 (80.8%) vaccinees and was child experienced swelling extending from shoulder to elbow. That child experienced localized pain at the injection sit

afebrile. For one child, swelling was assessed as grade 3 severity (i.e., prevented normal everyday activities and neces experiencing swelling, reaction began within 3 days of receipt of vaccine. Mean duration of swelling was 4 days (rang unpublished data, February and May 2000).

Pathogenesis of both substantial local reactions and limb swelling is unknown. In an analysis of data from the MAPT t >2 in. (>5 cm) after the fourth dose was associated with pertussis toxoid content of the vaccine administered; swelling aluminum content of the vaccine. Entire thigh swelling after the fourth dose was associated with diphtheria toxoid con to diphtheria, tetanus, or pertussis toxins were not predictive of this reaction. The inconsistent pattern of associations o the associations were a statistical artifact attributable to a limited sample size or to differential reporting of entire thigh

SUPPLEMENTAL ACIP RECOMMENDATIONS FOR USING DTaP VACCINES

Data are limited regarding differences in reactogenicity among currently licensed acellular pertussis vaccines. Increase reactions at the injection site with increasing dose number have been reported for all currently licensed DTaP vaccines receipt of fourth and fifth doses of acellular pertussis vaccines has been documented for mul tiple products from differ these reactions have generally not been solicited during safety studies, the frequency is unknown, and the absence of re receipt of particular DTaP vaccines. Additionally, in the majority of studies of adverse events after receipt of the fourth subset (a substantially limited subset in certain studies) of children who received the first three doses. Therefore, the ol reactions might have been influenced by selection biases of unknown direction and magnitude. Data are insufficient to from different manufacturers are associated with higher or lower frequencies of these reactions than receipt of a single data regarding the reactogenicity of DTaP vaccines when administered as a five-dose series are needed.

Whether children who experience entire limb swelling after a fourth dose of DTaP are at increased risk for this reactio to date indicate that the reactions are self-limited and in recognition of the benefits of the preschool dose of DTaP, a hi should not be considered a contraindication for receipt of the fifth dose of the DTaP series.

Parents or caregivers of children receiving the fourth and fifth doses of the DTaP series should be informed of the incr Although available data demonstrate that these reactions are self-limited and resolve without sequelae, they might be c (e.g., cellulitis) that require treatment. Therefore, providers must make decisions regarding evaluation and managemen vaccination on a case-by-case basis.

Interchangeable Use of Acellular Pertussis Vaccines

Children who began the series with DTaP at age 2 months began eligibility to receive a fifth dose of DTaP during mid- vaccinated on an accelerated schedule might have become eligible for the fifth dose before then. Data are insufficient t efficacy of using DTaP vaccines from different manufacturers in a mixed sequence. For this reason, the ACIP recomm DTaP vaccine should be used for all doses of the vaccination series. However, the vaccine provider might not know or previously administered to a child. Neither circumstance should present a barrier to administration of DTaP vaccine an be used to complete the vaccination series.

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Table

TABLE. Licensed DTaP vaccines by date of licensure for use among infants — United State

Date	Tradename	Manufacturer	Pertussis antigens
July 31, 1996	Tripedia®	Aventis Pasteur, Inc.	Inactivated pertussis toxin, 23 µg† Filamentous hemagglutinin, 23 µg†
December 30, 1996	ACEL-IMUNE®	Lederle Laboratories	Filamentous hemagglutinin, 34 µg† Pertactin, 1.6 µg Type 2 fimbriae, 0.8 µg
January 29, 1997	Infanrix®	SmithKline Beecham Biologicals	Inactivated pertussis toxin, 25 µg Filamentous hemagglutinin, 25 µg Pertactin, 8 µg
July 29, 1998	Certiva™	North American Vaccine, Inc.	Inactivated pertussis toxin, 40 µg

* Approved for use as the first four doses of the five-dose series, beginning at ages 2, 4, and 6 months.
† Amounts are approximate.

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